(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 266 038 A2

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: 87307666.5

(22) Date of filing: 28.08.87

(51) Int. Cl.[4]: A61N 5/06

(30) Priority: 29.10.86 JP 257345/86

(43) Date of publication of application: 04.05.88 Bulletin 88/18

(84) Designated Contracting States: DE FR GB IT NL SE

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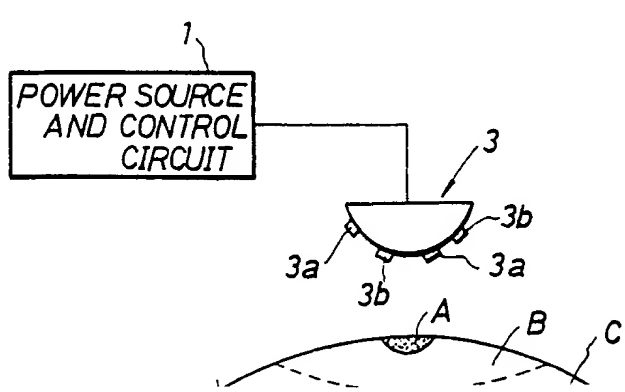
(54) **Apparatus for treatment of cancer with photodiode.**

(57) Apparatus for the treatment of a cancerous lesion part having absorbed and accumulated in advance therein a photosensitive substance with an affinity for tumors by irradiating a light energy from a light source to the cancerous lesion part comprising one or more first photodiodes (3a) adapted to excite the photosensitive substance from the ground state thereof to a singlet state of higher energy level and one or more second photodiodes (3b) adapted to exite an energy level of the photosensitive substance which has transited from the singlet state to a triplet state to a still higher energy level.

Fig.2



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APPARATUS FOR TREATMENT OF CANCER WITH PHOTODIODE

This invention relates to an apparatus for the treatment of a cancer by irradiating a cancerous lesion part in which is absorbed and accumulated in advance a photosensitive substance such as a hematoporphyrin derivative or a compound of phthalocyanine series having an affinity for tumors with light generated from a photodiode such as light-emitting diode or laser diode.

In recent years, studies on the application of the laser to the medical field have been gaining impetus. Particularly in the field of diagnosis and treatment of cancers, growing attention has been focused on the method for the treatment of cancer, which comprises administering a photosensitive substance such as a hematoporphyrin derivative to a cancer-carrying patient thereby causing the photosensitive substance to be selectively absorbed and accumulated in the tumorous area of the patient's body, irradiating the tumorous area with a laser beam thereby exciting the photosensitive substance into liberating a superoxide anion radical ($.O^{-}_{2}$), hydrogen peroxide (H_2O_2), a hydroxy radical (.OH), or a singlet oxygen ($^1O_2$), and utilizing the oxidizing power of the liberated radical or equivalent in destroying cancerous cells. Heretofore, a continuous wave laser beam such as argon-excited dye laser has been proposed to be used in this method. Since the energy of a laser beam injected into living tissues is exponentially attenuated relative to the depth of living tissues, however, a low-output continuous beam such as the aforementioned argon-excited dye laser has a small degree of energy penetration to the affected part and, consequently, is insuficiently powerful for treatment on a cancerous lesion of large size. In this field, therefore, emphasis is placed on the utilization or development of a laser beam source possessing a high output and a high degree of energy concentration. For example, Japanese Patent Application Laying-Open No. 59(1984)-40,869 discloses apparatus for the therapy and diagnosis of a cancer by the use of a pulsating laser beam in the place of a continuous wave laser beam. This treatment method and apparatus is expected to attain its full potential in the future in the sense of improving the degree of penetration of the energy of a laser beam to the interior of the lesion. It may be mentioned that any apparatus for the treatment of a cancer by the use of a laser beam source entails many problems concerning its practical utility because the laser emission device is large, expensive, troublesome in terms of maintenance and management, and devoid of versatility and because the high energy laser beam source required is liable to destroy normal cells as well as to the affected ones.

The inventors have conducted a diligent study in search of a breakthrough in respect of the state of affairs described above. They have consequently found that by using a photodiode as a light source for irradiation of a lesion which has absorbed and accumulated in advance therein a photosensitive substance with affinity for tumors and devising a method for excitation of the aforementioned photosensitive substance, treatment of a cancer can be efficiently carried out even when the continuous wave beam emitted from the photodiode possesses an extremely feeble energy which is some one tenth to some one ten thousandth of the energy of the laser beam. The present invention has been perfected as the result.

According to the present invention, there is provided apparatus for treatment of a cancerous lesion part having absorbed and accumulated in advance therein a photosensitive substance with an affinity for tumors, with light energy irradiated from a light source to said cancerous lesion part characterised in that said light source comprises one or more first photodiodes adapted to excite said photosensitive substance from the ground state thereof to a singlet state of a higher energy level and one or more second photodiodes to excite an energy level of said photosensitive substance which has transited from said singlet state to a triplet state to a still higher energy level.

Using the construction defined above, the apparatus of this invention for the treatment of a cancer is inexpensive and, as a whole, is small and light as compared with the therapeutic apparatus using a laser beam source. Whereas the conventional therapeutic apparatus using the laser beam source inevitably requires a patent to approach the apparatus by walking, the apparatus of the present invention can be applied to the affected part of the patient and enjoys many advantages from the standpoint of clinical therapy.

Moreover, the apparatus of the present invention utilizes a feeble energy radiation source as a light source and, therefore, is superior to the conventional countertype in terms of the safety from misoperation (erroneous irradiation). Further, as regards the effect of treatment, since the apparatus of this invention effects destruction and exfoliation of tumorous cells from the surface part thereof, it has the advantage that even when a tumor under treatment happens to be large, this apparatus is capable of bringing about complete cure of the tumor in a deep portion without adversely affecting the normal tissue adjacent to the tumor.

Now, the present invention will be described further in detail below with reference to the accompanying drawings.

Fig. 1 is a basic circuit diagram of apparatus of this invention for the treatment of a cancer.

Fig. 2 is a diagram showing the concept of the treatment of a cancerous lesion part by the use of the apparatus of the present invention.

Fig. 3a and Fig. 3b are diagrams illustrating typical embodiment of a light emission part of the apparatus of this invention.

Fig. 4 is a diagram illustrating another typical embodiment of the light emission part in the apparatus of this invention.

Fig. 5 is a diagram illustrating the relation between the time of irradiation with the beam from a photodiode and the proportion of surviving cells.

In Fig. 1 is shown the basic circuit diagram of the apparatus of this invention for the treatment of a cancer. As a power source 1, for example an AC-DC converter or, where the apparatus is intended as a portable version, a battery is used. A light emission part 3 comprises photodiodes 3a, 3b. One of these two photodiodes is used for exciting a photosensitive substance in the ground state (S_o) to a singlet state (S_n) and the other photodiode is used for exciting the energy level which has made the transition from the aforementioned singlet state to a triplet state (T) to a further higher level. The number of these photodiodes 3a, 3b and the manner of their disposition can be freely selected, depending on the position of the area for treatment on a patient's body, the size of the lesion part, the shpae of the lesion part, etc. A circuit part 2 is intended to protect or control an over-current to the light emission part 3. It is formed of a protective resistance, for example.

The basic circuit shown in Fig. 1, when necessary, may be provided with such an auxiliary device as a fan 4 adapted to remvoe from the light emission part 3 heat generated therein.

Fig. 2 is a diagram showing the concept of treatment of a cancerous lesion part by the use of the apparatus of the present invention. In Fig. 2, 1 denotes a power source part and an overcurrent protection part or control circuit part and 3 a light emission part respectively. In the light emission part 3, a plurality of photodiodes 3a, 3b are disposed. A stands for a cancerous lesion part, B for a peripheral part thereof, and C for a normal part respectively.

Preparatory to the actual treatment, a photosensitive substance such as a hematoporphyrin derivative is diluted with a pharmaceutically acceptable diluent and prepared otherwise and administered to a patient by intravenous injection, local injection, or abdominal injection, for example. Several days after the administration, the photosensitive substance is specifically absorbed and accumulated in the cancerous tissue and substantially ceases to exist in the normal tissue.

At this time, the apparatus of the present invention is operated so as to irradiate the cancerous lesion part with the beam issuing from the photodiodes or necessary treatment. The photodiodes 3a, 3b are suitably selected from light-emitting diodes or laser diodes, depending on the light absorption characteristic of the photosensitive substance being used. Where the photosensitive substance happens to be a hematoporphyrin derivative (HpD: product of Queen Elizabeth Hospital), for example, the combination of light emitting diodes of GaAsP having a wavelength of 630 nm and light emitting diodes of GaP have a wavelength of 690 nm proves to be a preferred choice. By irradiating the lesion part simultaneously with the beams from these two kinds of light emitting diodes, the photochemical reaction of the hematoporphyrin derivative is conspicuously enhanced and the effect of treatment consequently improved. Compounds of phthalocyanine series may be cited as other concrete examples of the photosensitive substance under discussion. This invention, however, is not restricted to the photosensitive substances mentioned above.

Fig. 3a and Fig. 3b illustrate a typical embodiment of the light emission part 3 in the apparatus of this invention for the treatment of cancer. Fig. 3a is a plan view of the light emission part 3 and Fig. 3b a cross section of the light emission part 3.

In Fig. 3a and Fig. 3b, 3a and 3b stand for photodiodes having different wavelengths. The conventional photodiodes can be utilized in their unmodified form. For the purpose of eliminating the directivity of emission, however, the leading end of each of the photodiodes may be cut out as indicated by the symbol D in Fig. 3b.

The structure of light emission part illustrated in Fig. 3a and Fig. 3b is intended for the treatment of such cancers as various epithelial cancers and mammary cancers. By suitably varying the shape and dimensions of the structure of light emission part, this structure may be adapted to permit treatment of such coeliac cancers as tumors in digestive organs like the gullet, the colon, and the stomach and cancers of the larynx.

Fig. 4 illustrates a typical applicator for the use of the apparatus for endotract or intracavitary treatment. In Fig. 4, 3a and 3b denote photodiodes different in kind from each other and 5 denotes a balloon made of a freely expansible and contractive material such as, for example, silicone rubber and adapted to enclose the photodiodes. This balloon 5 is provided with flow paths E and F for introducing and discharging a

coolant such as distilled water, physiological saline water, or olive oil which has a low level of light absorption. The balloon 5 advantageously functions to enable the output of the photodiodes to be increased, preventing the normal tissue in the neighborhood of the affected part from damage by burning, and ensuring fixation of the applicator to the affected path. Optionally, the flow path for the coolant may be formed inside the structure of photodiodes.

Now, the effect brought about by the use of the apparatus of this invention in the treatment of cancer will be described.

The test for the confirmation of this effect was performed as follows.

[Preparation of test specimen]

In a plastic dish 35 mm in diameter, 0.1 ml of a cancer cell (HeLa-S3) solution having a cell concentration of 2 × 10^5 per ml was placed and 2 ml of a culture medium was added; the resultant mixture was left standing at 37°C for 48 hours in an atmosphere containing 5% of carbon dioxide gas for culture of the cells. The culture medium was prepared by adding blood serum albumin in a concentration of 10% and Kanamycin (product of Meiji Seika Kaisha, Ltd.) in a concentration of 100 g/ml to an MEM-Eagle culture solution (product of GIBCO Corp.). After completion of the culture, the supernatant formed in the dish was removed and then 2 ml of a culture solution containing a hematoporpyrin derivative (HpD: product of Queen Elizabeth Hospital) in a concentration of 2 g/ml was introduced to continue the culture for two hours under the same conditions as mentioned above. Then, the supernatant formed in the dish at the end of the culture was discarded and the remaining culture broth was washed with 2 ml of an MEM-Eagle culture solution to remove the hematoporphyrin derivative which had not been absorbed and accumulated in the cells. By further adding 2 ml of culture medium to the cleaned remaining culture broth, there was obtained a test specimen.

[Irradiation test]

In a structure of light emission part illustrated in Fig. 3a and Fig. 3b, five photodiodes (TLS-154; product of Toshiba Limited) having a wavelength of 635 nm were used as 3a and four photodiodes (TLR-145; product of Toshiba Limited) having a wavelength of 690 nm were used as 3b, respectively. The aforementioned test specimen was placed in such a position that the photodiodes were separated by a distance of 8 mm from the upper side of the test specimen. It was irradiated with the beams of light emitted from the photodiodes with a supplied current of 18 mA, to find the relation between the time of irradiation and the ratio of surviving cells. The test specimens subjected to this test were taken as forming one group.

For comparison, an apparatus was formed by incorporating nine photodiodes of a wavelength of 635 nm as 3a and 3b in a similar structure of the light emission part. With this apparatus, a comparative test was carried out in the same manner as the method mentioned above. The test specimens subjected to this comparative test were taken as forming another group.

In the tests described above, a force air cooling duct was disposed between the plane of light emission and the test specimen for the purpose of preventing the temperature of the test specimen from rising, and the difference of temperature between the outlet and inlet thereof was kept below 0.4°C.

Table 1 shows the relation between the time of irradiation and the ratio of surviving cells in given two groups of test speciments relative to the control group (devoid of irradiation) as determined by the test with the apparatus of this invention and the comparative test.

Table 1

Time (hr)	3	6	18	24	48
Comparative test	1.0	1.0	0.88	0.91	0.81
This invention	1.0	0.98	0.84	0.75	0.41

By plotting the results of Table 1, there are obtained the two curves shown in Fig. 5.

The curve A represents the results of test obtained by the use of the apparatus of this invention and the curve B, those obtained by the use of the apparatus for comparative test.

In Fig. 5, the vertical axis is the scale of the ratio of surviving cells (%) in the respective groups relative to the control group (devoid of irradiation) and the horizontal axis the scale of time (hr) of irradiation.

The data of Fig. 5 demonstrates the effectiveness of the apparatus of this invention.

Claims

1. Apparatus for treatment of a cancerous lesion part having absorbed and accumulated in advance therein a photosensitive substance with an affinity for tumors, with light energy irradiated from a light source to said cancerous lesion part characterised in that solid light source comprises one or more first photodiodes (3a) adapted to excite said photosensitive substance from the ground state thereof to a singlet state of a higher energy level and one or more second photodiodes (3b) to excite an energy level of said photosensitive substance which has transited from said singlet state to a triplet state to a still higher energy level.

2. The apparatus according to claim 1, wherein a plurality of pairs of first (3a) and second (3b) photodiodes are disposed on a curved surface of a part-spherical shaped support member (3) on the peripheral surface of said support member (3) and projecting radially outwardly from said curved surface, any two randomly selected adjacent photodiodes being constituted by one of the first photodiodes (3a) and one of the second photodiodes (3b).

3. The apparatus according to claim 1, wherein a plurality of pairs of such first and second photodiodes are disposed on a side surface of one end of a flexible support member, in rows extending longitudinally of the flexible support member and transversely to said longitudinal direction, ones of the first and second photodiodes (3a, 3b) being positioned adjacent to one another and first and second photodiodes being surrounded with a freely expansible and contractive balloon (5) fastened at the opposite ends thereof to said support member, said balloon (3) being adapted to be provided with a flow path for introduction and discharge of a coolant.

4. The apparatus according to claim 3, wherein said flow path for introduction and discharge of a coolant is disposed inside said flexible support member.

5. The apparatus according to any one of claims 1 to 4, wherein said first and second photodiodes are respectively laser diodes.

6. The apparatus according to any one of claims 1 to 4, wherein said first and second photodiodes are respectively light-emitting diodes.

7. The apparatus according to claim 6, wherein said first photodiodes are light-emitting diodes of GaAsP type having a wavelength of 630 nm.

8. The apparatus according to claim 6, wherein said second photodiodes are light emitting diodes of GaP having a wavelength of 690 nm.

9. The apparatus according to any one of the preceding claims wherein said light source is connected to a power source (1) via a circuit (2) adapted to limit any overcurrent flowing to said light source.

10. The apparatus according to claim 9, wherein said circuit part comprises a protective resistance.

11. The apparatus according to claim 1, wherein said light source comprises a plurality of first and second photodiodes, which are alternately connected in series.

12. The apparatus according to any one of the preceding claims which is provided with cooling means adapted to remove heat generated in said light source.

Fig.1

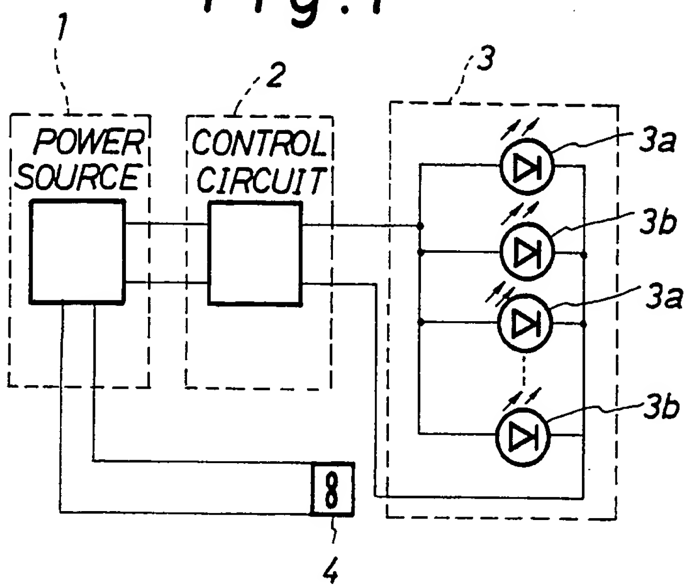

1
2
3
POWER SOURCE
CONTROL CIRCUIT
3a
3b
3a
3b
4

Fig.2

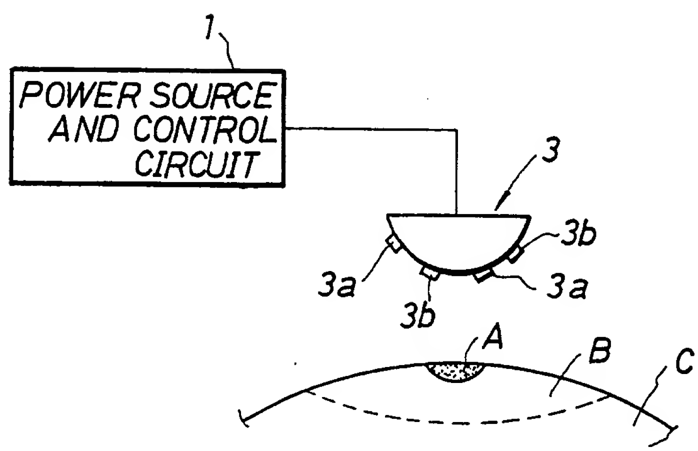

1
POWER SOURCE AND CONTROL CIRCUIT
3
3b
3a
3a
3b
A
B
C

Fig.3a

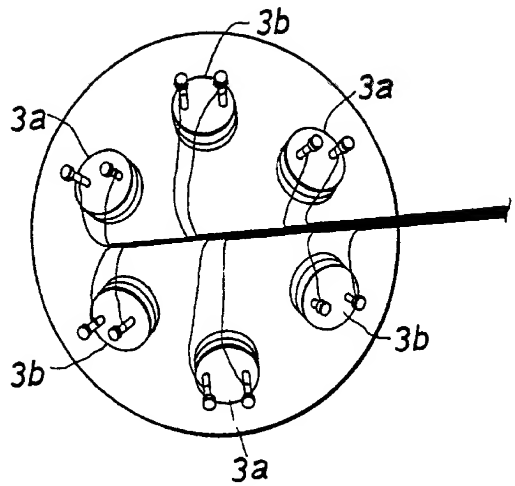


Fig.3b

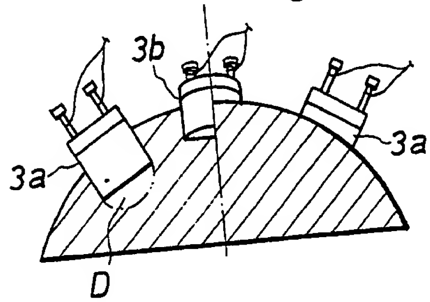


Fig.4

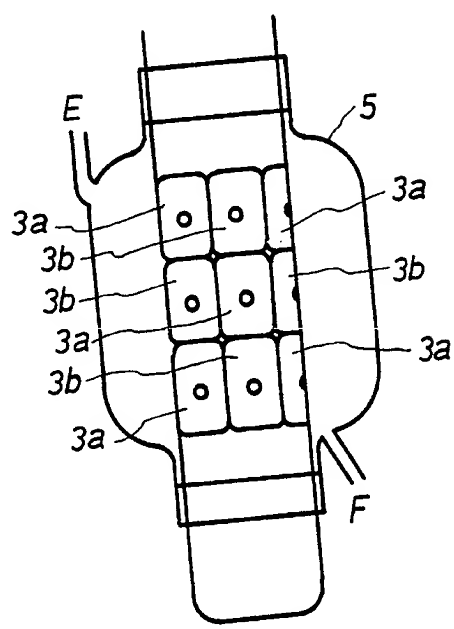
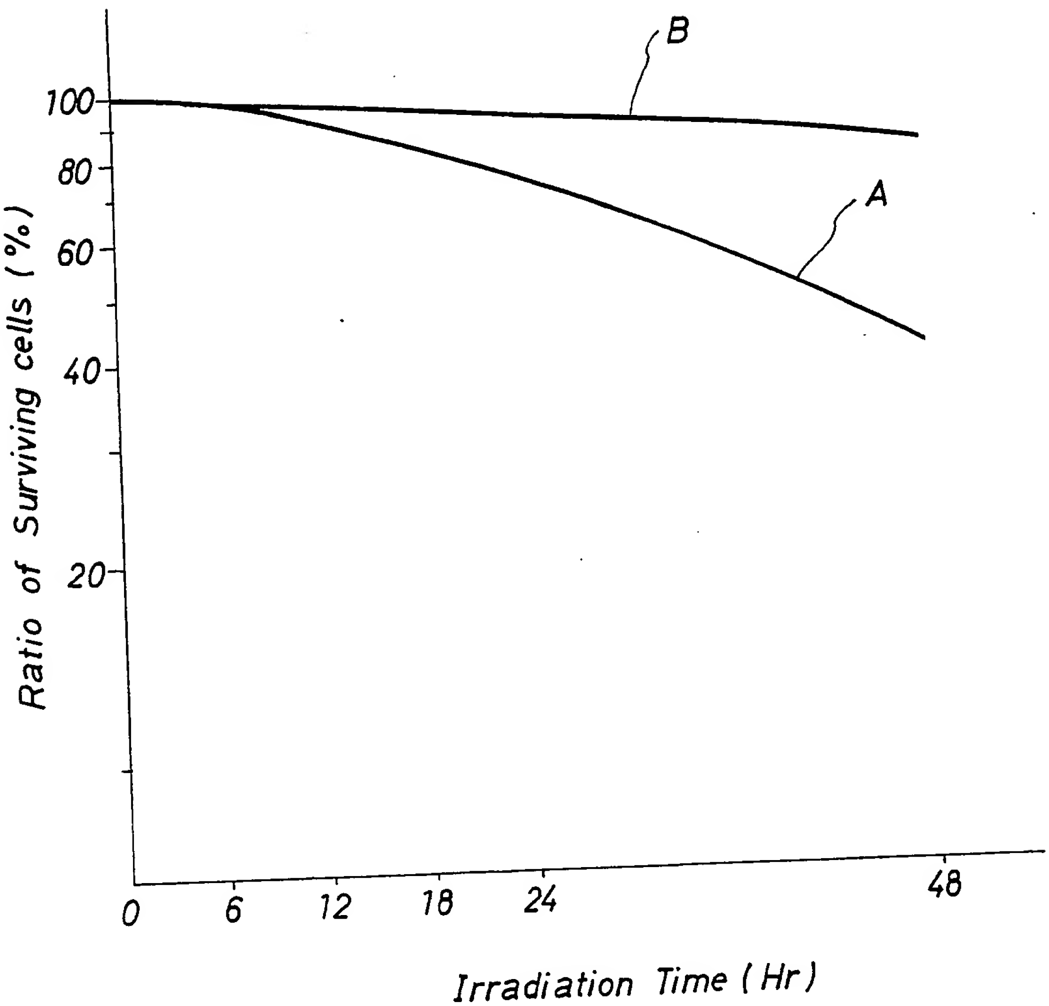


Fig.5


B
A
100
80
60
40
20
Ratio of Surviving cells (%)
0
6
12
18
24
48
Irradiation Time (Hr)